## Remarks/Arguments

The Examiner has maintained the 35 U.S.C. 103(a) objections raised in the previous Official Action and argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the administration of an aromatase inhibitor and a bisphosphonate as taught by Freyer, using specifically zoledronic acid as the bisphosphonate and letrozole as the aromatase inhibitor. In addition to maintaining the 35 U.S.C. 103(a) rejection, the Examiner states that the arguments regarding specific doses of zoledronic acid and letrozole are not commensurate with the claims. Applicants respectfully disagree.

It has been recently held by the United States Court of Appeals for the Federal Circuit that the nature of bisphosphonates are unpredictable, Procter & Gamble Co. vs. Teva Pharma (Fed. Cir. 2009). Applicants maintain that, at the time of the publication of Freyer et al. and Iqbal et al. it would not have been common practice or even general knowledge among one of ordinary skill in the art to combine the methods of treatment as taught by Freyer et al. and Iqbal to arrive at the inventions recited in the claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck,* 974 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991). Since all of the references cited published before the Food and Drug Administration approved zoledronic acid, under the trademark ZOMETA, it would not have been common practice or even general knowledge among one of ordinary skill in the art to combine the methods of treatment as taught by Freyer et al. and Iqbal to arrive at the claimed combination. The missing descriptive matter in Freyer et al. and Iqbal et al. is the motivation to use zoledronic acid since zoledronic acid had not been approved yet for the treatment of bone metastases. Furthermore, it would not have been obvious to one of ordinary skill in the art to have combined the aromatase inhibitor and bisphosphonate as taught by Freyer and included the medication as package with instructions since zoledronic acid was not approved for the treatment of bone metastases. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). None of the references cited make clear that the missing descriptive matter is necessarily present and such missing descriptive matter would not have been recognized by a person of ordinary skill. Therefore, the recited combination, methods of treatment in the present set of claims are nonobvious over the prior art. Reid does not correct the deficiencies of Freyer et al. and Iqbal et al.. Reid does not teach or suggest combining zoledronic acid with an aromatase inhibitor to treat bone loss associated with the administration of an aromatase inhibitor. As stated above, Example 6 of the specification

describes the unexpected result of zoledronic acid protecting against cancellous bone loss, corical thinning and reduction of bone strength induced by daily oral administration of letrozole.

Furthermore, Applicants respectfully submit that, as evidenced by various publications available at the time the instant application was filed, success was not anticipated for employing the administration of an aromatase inhibitor and a bisphosphonate as taught by Freyer, using specifically zoledronic acid as the bisphosphonate and letrozole as the aromatase inhibitor. Thus, "obvious to try", which appears to be the Office's rationale for obviousness, is not appropriate in the instant situation. *See id; accord In re Kubin,* 561 F.3d 1351, (Fed. Cir. 2009) (discussing the Supreme Court's analysis of "obvious to try", which limits its application to situations having a "finite number of identified, predictable solution" or when "the improvement is [no] more than the predictable use of prior art elements according to their established functions."); *accord In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Applicants argue none of the cited references described the unexpected results found by combining letrozole with zoledronic acid. Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

The specific doses as exemplified in the Examples are commensurate with the claims. The claims define using an "effective amount" of zoledronic acid. A person of ordinary skill in the art could determine the specific values for the effective amount based on the claims, *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). Example 6, starting on page 50 of the specification describes the effectiveness of intravenous administration of zoledronic acid in preventing the bone loss and reduction of mechanical properties induced by aromatase inhibition or surgical ovariectomy in rats. The results showed a single iv injection of 0.8 μg/kg zoledronic acid delayed bone loss significantly for 24 weeks in patients treated with letrozole with the highest dose being full protective over the entire 24-week duration of the study, page 51 lines 6-10 of the specification. The findings of this study were summarized on page 52 of the specification:

> Discussion: Our data indicates for the first time that in rats, Zol dose-dependently protects against cancellous bone loss, corical thinning and reduction of bone strength induced by daily oral letrazole, at a dose of 20μg/kg, fully protects against letrozole induced bone loss for at least 24 weeks.

Applicants respectfully request the obviousness rejection be withdrawn from consideration. Entry of this Response is respectfully requested.

Respectfully submitted,

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